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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,042	09/26/2001	Ralph Weichselbaum	27373/36638A	1056

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/964,042	WEICHSELBAUM ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10-13 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/21/2007 has been entered.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 1-5, 10-13 and 16 are currently pending and are examined herein.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 10-13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Advani (1997; Int. Journ. Oncol. Rad. Biol. Phys, previously of record) in view of Carroll et al. (Ann. Surg. 1996, previously of record).

The instant claims are drawn to a method for reducing a non-central nervous system tumor mass by administering an attenuated HSV to a subject having cancer wherein the HSV genome has been modified in an inverted repeat region such that the HSV has only one active gamma(1)34.5 gene, wherein the HSV is administered in an amount effective to reduce the mass of the tumor mass.

Advani (1997) is an abstract that teaches "Human U-87MG glioma cells were grown in the hind limb of athymic mice... and infected with... [HSV] R7020... the tumors were harvested... 14 days after viral injection." Furthermore, Advani teaches, "Herein we demonstrate radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in treating glioma xenografts and a potential therapeutic motif in the treatment of gliomas." Therefore, Advani (1997) clearly teaches a method for reducing tumor mass comprising direct delivery of the attenuated HSV (HSV R7020) to the tumor.

Advani does not explicitly teach that the attenuated HSV virus could be used to treat a non-CNS tumor in vivo.

Carroll teaches treatment of non-CNS tumor using an attenuated HSV (hrR3). Specifically, Carroll teaches a method for treating colon carcinoma liver metastasis by administering an attenuated HSV directly to cells the tumor (e.g., see abstract).

Therefore, it would he been prima facie obvious at the time of invention that the method taught by Advani would have also been able to treat a non-CNS tumor such as a colon carcinoma liver metastasis in an animal or human, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the method of Advani to treat a non-CNS cancer because Carroll teaches that attenuated HSVs can be used to treat non-CNS-type tumors. Furthermore, the in vitro findings that taught by the Advani references are indicative of an expectation of success for directly administering the vectors to tumors in vivo.

Response to Arguments

Applicant's arguments filed 2/21/2007 have been fully considered, but are not persuasive.

Applicants contend that Advani (1997), does not show that R7020, or R3616 would be useful in treating the xenografts that the R7020 and R3616 are administered to because the graphs showing viral yield as a function of time post-infection show that the yields of each of R3616 and R7020 drop to zero prior to day 14, a day on which xenograft tumors were still being harvested from mice. Applicants assert that in view of this, all of the viral therapeutic is apparently lost from the mice prior to eradication of the xenograft tumor and Advani (1997) does not disclose or suggest that R7020 (or any other HSV) would be effective in treating a CNS tumor or a non-CNS tumor.

In response, it is noted that Advani does teach administration of HSV R7020 and R3616 directly to a glioma tumor that was xenografted to a mouse limb. Advani specifically teaches that it was already known that combining IR with R3616 "significantly increased glioma

xenograft eradication compared to IR or virus alone." Advani teaches, "One hypothesis is that IR induces cell factors that contribute to augment viral replication thereby increasing the efficacy of attenuated HSV-1." As such, it is clear that an attenuated HSV-1 (R3616) was already known as being capable of treating glioma tumors *in vivo*. However, the mechanism by which IR increased HSV-1 effect had not been determined, but Advani hypothesized that the increased effect was due to IR augmenting viral replication. In other words, increasing replication of the attenuated virus would be one way to increase the anti-tumor effects of the attenuated HSV-1, thus increasing replication of the virus would increase should increase the efficacy of the HSV treatment. In these experiments, Advani attempted to test this hypothesis. It is noted that Advani teaches that irradiation was performed on day 1 and day 2 and tumors were harvested periodically up to 14 days after the first irradiation. Advani recognized that "Our results indicate IR augments the amount of virus recovered from human glioma xenografts for up to 3 days post IR." Therefore, Applicants argument that the viral therapeutic is apparently lost from the mice prior to eradication of the xenograft tumor is not persuasive because: (1) Advani demonstrates an increase in viral replication when IR is used in combination with the HSVs, indicating that at least for the period of time that the virus is replicating, the viral replication would be treating the tumor which would result in reduction of the tumor mass; and (2) since IR was performed only on days 1 and 2, the fact the viral replication was at 0 on day 14 merely indicates that the effect of the IR treatment had been lost over time, it does not indicate that the treatment would not be effective for reducing tumor mass. Furthermore, the teaching of Advani that, "[the results] demonstrate radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in <u>treating glioma xenografts</u> and a potential therapeutic motif in the

treatment of gliomas" is a clear indication that the treatment is useful for treating (i.e., reducing the mass of) glioma tumors.

Applicants contend that one of skill in the art would understand that a method of treating any tumor would need to provide a safe therapeutic in addition to providing an effective therapeutic, and Advani says nothing about the effect that HSV R7020 might have on healthy cells *in vivo*.

In response, it is noted that Advani specifically teaches, "to reduce normal tissue toxicity of HSV in glioma therapy, viruses must be attenuated" which demonstrates that Advani recognizes that cytotoxicity is an issue and attenuating the virus must be done because of the cytotoxicity. The virus used by Advani are attenuated which would decrease viral cytotoxicity. Furthermore, although Advani does not explicitly discuss the effect of the treatment on the healthy cells of the mouse, it is noted that since the tumors were harvested up to 14 days after treatment began, the mouse must have survived for at least 14 days after treatment began which demonstrates that the attenuated virus treatment was not lethal. Furthermore, the fact that the attenuated virus may have some cytotoxic effect on normal tissue does not indicate that the treatment would not be effective for reducing tumor mass, which is the requirement of the claims.

Applicants argue that the fact the attenuated HSV replicates in glioma cells is unremarkable. Applicants point out that Advani does not teach treating non-CNS or CNS tumors

in vivo, and that Carroll does not fairly suggest using the attenuated HSV for treating non-CNS tumors.

In response, it is acknowledged Advani does not tech treating non-CNS tumors. The Examiner respectfully disagrees with Applicants assertion that Advani does not teach treatment of CNS tumors, for the reasons indicated above. Furthermore, as indicated above, Carroll teaches that an attenuated HSV (hrR3) can be used as to treat non-CNS tumors, demonstrating the attenuated HSV are effective for treating non-CNS tumors. Since Advani teaches that R7040 and R3616 are attenuated HSVs that are effective for treating tumors, one of ordinary skill in the art would recognize that the HSV of Advani is simply another type of attenuated HSV which could be used to treat a non-CNS tumor (as taught by Carroll).

Applicants argue that Carroll does not teach direct delivery of the HSV to a tumor.

In response, as acknowledged by Applicants, Carroll teaches intrasplenic administration of tumor cells followed by intrasplenic administration of an attenuated HSV. By administrating the tumor cells and the HSV intrasplenically, both the cells and the HSV would be administered to the same location. This would necessarily result in the direct delivery of the vector to the tumor cells. It is acknowledged that this would not constitute a intratumoral administration, but such is not asserted by the Examiner.

Applicants argue that the Examiner's generalization of Carroll is improper. Applicants contend that the HSV used by Carroll (hrR3) has an inactivated U_L39 which would be incapable of expressing ICP6 and not any attenuated HSV would satisfy this criterion. Applicants further

contrast hrR3 with R7020, indicating that the hrR3 is more attenuated then R7020. Applicants argue that the attenuation of R7020 relative to hrR3 means that one of ordinary skill in the art would not have expected the results obtained with R7020 in the CNS context to be extendable to the non-CNS context.

In response, it is acknowledged that hrR3 and R7020 are not the same and that R7020 is less attenuated than hrR3. However, both are recognized in the art as being attenuated HSVs which can be used to treat tumors. None of Applicants arguments address whether or not the R7020 would be able to kill non-CNS tumor cells. In fact, since the R7020 is less attenuated, one of ordinary skill in the art would most likely expect R7020 to be more toxic than hrR3. Therefore, one of skill in the art would most likely reasonably expect R7020 to be at least as effective as hrR3 at killing tumor cells, although there may be higher chance that that R7020 could also be toxic to non-tumor cells. However, it is noted that Advani recognizes that to reduce normal tissue toxicity, viruses must be attenuated. Furthermore, R7020 is an attenuated HSV. Also, the fact that the R7020 virus may have some cytotoxic effect on normal tissue does not indicate that the treatment would not be effective for reducing tumor mass, which is the requirement of the claims.

Therefore, Applicants' arguments, as they apply to the instant rejection(s), are not persuasive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER
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